

Longitudinal associations of multiple physical symptoms with recurrence of depressive and anxiety disorders

Article (Accepted Version)

Dijkstra-Kersten, Sandra M A, Sitnikova, Kate, Terluin, Berend, Penninx, Brenda W J H, Twisk, Jos W R, van Marwijk, Harm W J, van der Horst, Henriette E, van der Wouden, Johannes C and Unset (2017) Longitudinal associations of multiple physical symptoms with recurrence of depressive and anxiety disorders. *Journal of Psychosomatic Research*, 97. pp. 96-101. ISSN 0022-3999

This version is available from Sussex Research Online: <http://sro.sussex.ac.uk/id/eprint/72743/>

This document is made available in accordance with publisher policies and may differ from the published version or from the version of record. If you wish to cite this item you are advised to consult the publisher's version. Please see the URL above for details on accessing the published version.

Copyright and reuse:

Sussex Research Online is a digital repository of the research output of the University.

Copyright and all moral rights to the version of the paper presented here belong to the individual author(s) and/or other copyright owners. To the extent reasonable and practicable, the material made available in SRO has been checked for eligibility before being made available.

Copies of full text items generally can be reproduced, displayed or performed and given to third parties in any format or medium for personal research or study, educational, or not-for-profit purposes without prior permission or charge, provided that the authors, title and full bibliographic details are credited, a hyperlink and/or URL is given for the original metadata page and the content is not changed in any way.

LONGITUDINAL ASSOCIATIONS OF MULTIPLE PHYSICAL SYMPTOMS WITH RECURRENCE OF DEPRESSIVE AND ANXIETY DISORDERS

Sandra M.A. Dijkstra-Kersten MSc ¹

Kate Sitnikova MSc ¹

Berend Terluin PhD, MD ¹

Brenda W.J.H. Penninx PhD ^{2, 3, 4}

Jos W.R. Twisk⁵ PhD

Harm W.J. van Marwijk PhD, MD ⁶

Henriette E. van der Horst PhD, MD ¹

Johannes C. van der Wouden PhD ¹

¹ Department of General Practice and Elderly Care Medicine, Amsterdam Public Health research institute, VU University Medical Center, Amsterdam, the Netherlands.

² Department of Psychiatry, Amsterdam Public Health research institute, VU University Medical Center, GGZ inGeest, Amsterdam, the Netherlands.

³ Department of Psychiatry, Leiden University Medical Center, the Netherlands.

⁴ Department of Psychiatry, University Medical Center Groningen, the Netherlands.

⁵ Department of Epidemiology and Biostatistics, Amsterdam Public Health research institute, VU University Medical Center, Amsterdam, the Netherlands.

⁶ Manchester Academic Health Sciences Centre and NIHR School for Primary Care Research, Manchester, UK.

Corresponding author:

Sandra Dijkstra-Kersten

Department of General Practice and Elderly Care Medicine

VU University Medical Center

E: s.kersten@vumc.nl

T: +31 20 444 8030

Attn. Sandra Dijkstra-Kersten

Van der Boechorststraat 7

1007 MB Amsterdam, the Netherlands

ABSTRACT

Objective: To examine longitudinal associations of multiple physical symptoms with recurrence of depressive and anxiety disorders.

Methods:

Follow-up data of 584 participants with remitted depressive or anxiety disorders were used from the Netherlands Study of Depressive and Anxiety disorders. Multiple physical symptoms were measured at baseline (T1) and two-year follow-up (T2) by the Four-Dimensional Symptom Questionnaire (4DSQ) somatization subscale. Recurrence of depressive and anxiety disorders was assessed at two-year (T2) and four-year (T4) follow-up with the Composite International Diagnostic Interview. Logistic Generalized Estimating Equations were used to examine associations of multiple physical symptoms with recurrence of depressive and anxiety disorders. Depressive (IDS-SR) and anxiety symptoms (BAI), and other relevant covariates were taken into account.

Results:

Multiple physical symptoms were significantly associated with recurrence of depression (OR=1.04, 95%CI=1.00-1.08), anxiety (OR=1.07, 95%CI=1.03-1.12), and depressive or anxiety disorders (OR=1.06, 95%CI=1.02-1.10), on average over time. Odds ratios did not change substantially when the IDS-SR mood-cognition and BAI subjective scale were included as covariates.

Conclusion:

The presence of multiple physical symptoms was positively related to recurrence of depressive and anxiety disorders, independent of depressive and anxiety symptoms. Knowledge of risk factors for recurrence of depressive and anxiety disorders, such as the presence of multiple physical symptoms, could provide possibilities for better targeting interventions to prevent recurrence.

Key words:

Anxiety disorder, Depressive disorder, Multiple physical symptoms, Somatization, Recurrence

INTRODUCTION

Depressive and anxiety disorders are a leading cause of disease burden, mainly due to their recurrent nature [1-3]. The National Institute of Mental Health Collaborative Depression Study, reported recurrence rates of depression of 25-40% after two years and up to 85% after fifteen years [4, 5].

Strategies to reduce the burden of depressive and anxiety disorders should not only focus on treatment of acute episodes but also on prevention of recurrence [6]. Knowledge of risk factors for recurrence of depressive and anxiety disorders could provide a rationale for such preventive interventions or long-term treatment and allow possibilities for better targeting care [7].

Hardeveld et al. [8] found two main predictors of recurrence of depressive disorders in their systematic review: the number of previous depressive episodes and subclinical residual depressive symptoms after recovery from the last episode. However, they concluded that knowledge of predictors of recurrence of depressive disorders is still incomplete. They recommended more prospective research, particularly in the general population, to gain conclusive knowledge of predictors of recurrence of depressive disorders.

Putative predictors of recurrence of depressive and anxiety disorders can be identified by looking at predictors of depressive and anxiety disorders in general. One of the factors related to co-occurrence, onset and course of depressive and anxiety disorders is the presence of multiple physical symptoms [9-14]. Despite these relationships, it is poorly understood how multiple physical symptoms impact the recurrence of depressive and anxiety disorders in remitted patients. A small study [15] concluded that a sustained high number of (medically unexplained) physical symptoms was predictive of subsequent recurrence in remitted, recurrently depressed patients. However, so far, little research has been performed on this association.

This study, therefore, examined the longitudinal association of multiple physical symptoms with recurrence of depressive and anxiety disorders in a prospective cohort study. Furthermore, as symptoms of depression and anxiety are a main predictor of recurrence of depressive and anxiety disorders, we took residual depressive and anxiety symptoms into account and examined whether excluding somatic features of residual depressive and anxiety symptoms altered our results.

METHODS

Design

This study used four-year prospective data from the Netherlands Study of Depressive and Anxiety Disorders (NESDA)[16]. NESDA is an ongoing cohort study that aims to investigate the etiology, course and consequences of depressive and anxiety disorders. At baseline (2004-2007) 2981 participants aged 18 through 65 years were included, consisting of healthy controls; persons with a

prior history of a depressive or anxiety disorder; persons with a high risk because of a family history or subthreshold depressive or anxiety symptoms; and persons with a current depressive or anxiety disorders. Participants were recruited in three settings: the community ($n = 564$), primary care ($n = 1610$), and mental health services ($n = 807$). Exclusion criteria were a primary diagnosis of obsessive compulsive disorder, bipolar disorder or severe addiction disorder, and not being fluent in Dutch. Assessments consisted of a diagnostic psychiatric interview, questionnaires, and a medical assessment. For the current analyses, we used the assessments at baseline (T0), two-year follow-up (T2), and four-year follow-up (T4). All participants provided written informed consent and the research protocol was approved by the ethical review boards of participating universities. The design and sampling procedure of NESDA have been described in more detail [16].

Study population

Participants who had a depressive (major depressive disorder or dysthymia) or anxiety (panic disorder, social phobia, generalized anxiety disorder or agoraphobia) episode in the past but were in remission at T0 for at least six months were selected for our study ($n = 628$). Current and lifetime depressive and anxiety disorders were examined using the DSM-IV based Composite International Diagnostic Interview (CIDI, version 2.1) [17].

Participants who did not participate in any of the follow-up measurements were excluded from analyses ($n = 40$). Additionally, participants without data on the main determinant (multiple physical symptoms) on any of the assessments were excluded ($n = 4$). This resulted in a study sample of 584 participants. Non-respondents ($n = 44$) were more often males (54.5%), compared to the study sample (28.9%, $p = .02$). No significant differences were found for any of the other study sample characteristics.

Measures

Recurrence of depressive and anxiety disorders

We defined recurrence of depressive and anxiety disorders as the occurrence of a new depressive or anxiety disorder episode between T0 and T2, and between T2 and T4, respectively, according to CIDI diagnostic criteria.

Multiple physical symptoms

The presence of multiple physical symptoms was assessed at T0 and T2 by the somatization subscale of the Four-Dimensional Symptom Questionnaire [18, 19]. Somatization is defined as “the tendency to experience and communicate somatic distress and symptoms unaccounted for by pathological findings, to attribute them to physical illness, and to seek medical help for them” [20]. The 4DSQ somatization subscale operationalizes somatization as a high number and frequency of physical

symptoms and does not establish whether physical symptoms are medically unexplained or whether participants sought help for these symptoms. Therefore, in this study we used the 4DSQ somatization subscale to assess multiple physical symptoms, regardless of their being presented to a doctor or being explained.

The 16 items of the 4DSQ correspond to symptoms participants may have had in the past week (e.g. 'during the past week did you suffer from dizziness; painful muscles; headache?') and are scored on a five-point Likert scale ('no', 'sometimes', 'regularly', 'often', and 'very often or constantly'). Item scores were recoded into a 3-point scale ('no', 'sometimes', and 'regularly' to 'very often or constantly') and summed to obtain a total score (0-32). An overall score of 11 or higher is indicative of an elevated level of somatization and risk of impaired functioning [18]. The 4DSQ somatization subscale has been validated against various measures (e.g. SCL-90 somatization subscale and GP's diagnoses) in a variety of samples, including psychiatric, occupational, and primary care samples [18, 21].

Covariates

Demographic characteristic

Age, gender and number of years of education were assessed at T0 by self-report questionnaires.

Chronic somatic diseases

Chronic somatic diseases may be related to the reporting of physical symptoms and the occurrence of depressive and anxiety disorders. Therefore, we took the number of chronic somatic diseases into account in our analyses. At T0, participants were asked whether they suffered from any of the chronic somatic diseases mentioned in the interview and whether they received medication or treatment for these diseases. The following diseases were surveyed: lung disease, heart diseases or infarction, diabetes, stroke, osteoarthritis, cancer, ulcer, intestinal disorders, liver disease, epilepsy and thyroid gland disease. Answers were categorized as 'no chronic somatic disease', 'one chronic somatic disease' or 'two or more chronic somatic disease'.

Psychosocial characteristics

As several studies have indicated that neuroticism, mastery and childhood trauma may be associated with the presence of multiple physical symptoms as well as with (recurrence of) depressive and anxiety disorders, these variables were taken into account as covariates [7, 8, 22-24].

Neuroticism was measured by the Neuroticism domain of the NEO-FFI [25]. This domain consists of 12 items (e.g. "I am not a worrier"), which are scored on a five-point Likert scale. Item scores were summed to obtain a total score, ranging from 12 to 60.

Mastery, the extent to which a person perceives himself to be in control of events or ongoing situations, was measured by the Pearlin Mastery scale [26]. Participants rated their agreement with five statements on a five-point Likert scale. A sum score was calculated (5-25), with a higher score indicating more feelings of mastery.

Childhood trauma was assessed retrospectively at T0 by the Nemesis Childhood Trauma Interview [27, 28]. In this interview, questions were asked about the frequency of emotional neglect, psychological abuse, physical abuse, and sexual abuse before the age of 16. First, answers were recoded into three categories for each question (0 = never; 1 = 'once', 'sometimes'; 2 = 'regularly', 'often', 'very often'). Second, the sum of frequency of childhood trauma (0-8) was calculated for each participant, after which the total score was categorized into five categories (0 = 0, 1-2 = 1, 3-4 = 2, 5-6 = 3, 7-8 = 4)[27].

Clinical characteristics

Subclinical residual depressive symptoms and the number of previous depressive episodes are the strongest predictors of recurrence of depressive disorders [7, 8, 24]. Also, the recency of the last depressive or anxiety episode may be related to the risk of recurrence as well as the reporting of physical symptoms. These clinical characteristics were, therefore, considered as covariates. Number of previous depressive episodes and recency of the last depressive or anxiety episode were assessed at T0 with the CIDI.

Subclinical residual depressive and anxiety symptoms at T0 were assessed by the Inventory of Depressive Symptomatology-Self Report (IDS-SR₃₀) [29, 30] and the Beck Anxiety Inventory (BAI), respectively. The BAI is a validated, 21 item self-report instrument which measures the overall severity of anxiety [31, 32]. Many instruments measuring depressive and anxiety symptoms tend to include some somatic symptoms such as fatigue and palpitations, as these are part of diagnostic criteria for depressive and anxiety disorders. For this reason, we also measured depressive and anxiety symptoms by means of the BAI subjective scale [32], which consists of seven items covering subjective and cognitive features of anxiety, and the 11-item IDS-SR mood-cognition subscale, which covers symptoms of depressed mood and cognitions [33]. In contrast, the BAI somatic subscale only covers somatic features of anxiety and the IDS-SR anxiety-arousal subscale covers symptoms of anxiety, somatic symptoms and somatic agitation/slowing.

Statistical analyses

Descriptive statistics were used to describe the sample characteristics at T0. A missing value analysis was done to assess whether missing values were at random.

Logistic Generalized Estimating Equations (GEE) were used to examine the longitudinal association of multiple physical symptoms with recurrence of depressive and anxiety disorder. GEE takes the

dependency of the repeated observations of the same participant into account. A time-lag model was used in which the presence of multiple physical symptoms (continuous and dichotomous) was assessed at T0 and T2, and recurrence of depressive and anxiety disorders was assessed at T2 and T4 (see Figure 1). Separate analyses were performed with recurrence of depressive disorders, recurrence of anxiety disorders, and recurrence of depressive or anxiety disorders as the outcome, respectively, and were adjusted for covariates in a stepwise manner. First, we adjusted for socio-demographic characteristics (age, gender and education level). Thereafter, number of chronic somatic disorders, recency of the last depressive or anxiety episode, number of previous depressive episodes, subclinical depressive (IDS-SR) or anxiety symptoms (BAI) at T0, neuroticism, mastery and childhood abuse were entered in the model as fixed factors. We repeated the analyses replacing the BAI and IDS-SR by the BAI subjective scale and IDS-SR mood-cognition subscale because these subscales contain no somatic features of depressive and anxiety disorders.

Lastly, participants who reported a depressive or anxiety episode during the first period (T0-T2) may still have been depressed or anxious in the second period (T2-T4), which could imply a chronic depressive or anxiety disorder. Therefore, sensitivity analyses were performed in which we excluded the assessments in the second period of participants who reported a depressive or anxiety episode at T2 (1 month recency) as well as between T2 and T4 ($n = 45$).

Analyses were performed with SPSS (version 22) statistical software. Statistical significance was tested two-sided at a level of $p < .05$.

RESULTS

Characteristics of the study sample at T0 are given in Table 1. Mean age was 44.2 (12.9) years, 71% of the participants was female. At T0, 29% scored ≥ 11 on the 4DSQ somatization subscale, which is an indication of impaired functioning. Median 4DSQ score was 6. At T2, 23% of participants scored above the cut-off score of 11. Thirty-eight percent ($n = 222$) of the study sample reported an elevated 4DSQ score (≥ 11) at one or more assessments and 59 of these participants scored ≥ 11 at all three assessments.

Missing data

We evaluated whether missing values of the main determinant and outcome variables were related to each other. In our study sample, participants with a missing 4DSQ score at T2 ($n = 21$; $\chi^2 (1) = 11.18$, $p = .001$) reported a depressive or anxiety episode more often at T4. Participants with missing information on depressive or anxiety disorders at T2 ($n = 10$; $\chi^2 (1) = 6.20$, $p = .013$) reported a depressive or anxiety episode more often at T4. Also, participants without information on depressive or anxiety disorders at T4 reported a 2.74 ($n = 50$; $t (578) = -3.29$, $p = .001$) and 2.75 ($n = 47$; $t (558) =$

-3.34, $p = .001$) points higher 4DSQ score at T0 and T2, respectively, and reported a depressive or anxiety episode more often at T2 ($n = 50$; $\chi^2(1) = 4.16$, $p = .041$). Missing data on other variables were not related to the main determinant and outcome.

Longitudinal associations between multiple physical symptoms and recurrence of depressive and anxiety disorders

Between the T0 and T2 assessment, 169 of 574 participants (29.4%) developed a depressive or anxiety episode; 121 of 574 (21.1%) a depressive episode and 95 of 574 (17.4%) an anxiety episode. Between T2 and T4, 138 of 534 participants (25.8%) reported a depressive or anxiety episode; 93 (17.4%) a depressive episode and 73 (13.7%) an anxiety episode. If we exclude the 169 participants who had had a depressive or anxiety episode in the first period, 61 of 376 participants (16.2%) had a new episode between T2 and T4.

Overall, 33.3% of the participants with a 4DSQ score <11 at T0 reported a depressive or anxiety episode between T0 and T4, compared to 58.3% of the participants with an elevated (≥ 11) 4DSQ somatization score.

GEE analyses (Table 2) showed that multiple physical symptoms were significantly associated with recurrence of depressive disorder (OR = 1.04, 95%CI = 1.00 to 1.08), anxiety disorder (OR = 1.07, 95%CI = 1.03 to 1.12), and depressive or anxiety disorders (OR = 1.06, 95%CI = 1.02 to 1.10), on average over time. An odds ratio of 1.06 can be interpreted as follows: every unit increase in 4DSQ score results in a 6% higher odds of recurrence of depressive or anxiety disorders, within and between subjects. Changing the complete IDS and BAI by the IDS mood and cognition subscale and the BAI subjective subscale did not change these results substantially.

Also, an elevated 4DSQ score (≥ 11) was associated with a higher risk of recurrence of depressive and anxiety disorders (Table 3 Appendix, adjusted for sociodemographics; depression: OR = 2.39, 95%CI = 1.69 to 3.40; anxiety: OR = 2.24, 95%CI = 1.54 to 3.25; depression or anxiety: OR = 2.30, 95%CI = 1.67 to 3.17). However, these associations were attenuated after adjusting for covariates such as depressive symptoms and neuroticism (depression: OR = 1.36, 95%CI = 0.88 to 2.10; anxiety: OR = 1.42, 95%CI = 0.90 to 2.24; depression or anxiety: OR = 1.48, 95%CI = 0.98 to 2.25).

DISCUSSION

Main findings

This prospective study showed that multiple physical symptoms were positively associated with recurrence of depressive and anxiety disorders, even when residual depressive and anxiety symptoms were taken into account.

Our findings in light of existing literature

So far, research on the association between multiple physical symptoms and recurrence of depressive or anxiety disorders is limited. A study [15] showed that a sustained high number of (medically unexplained) physical symptoms was related to recurrence in remitted, recurrently depressed patients. Associations between multiple physical symptoms and the course of depressive disorders have been studied more extensively. A systematic review by Huijbregts et al. [12] found consistent evidence for a negative association between the presence of physical symptoms and treatment response in currently depressed patients. Also, a primary care study found that patients with a chronic course had more severe physical symptoms at baseline compared to remitted patients [14], while a study using the NESDA data [13] concluded that somatic clusters of persistent cardiopulmonary, gastrointestinal, and general symptoms were related to persistence of depressive disorders, when two or more of these clusters were present.

Overall, our results did not change substantially when we adjusted for residual depressive and anxiety symptoms and used the IDS mood-cognition and BAI subjective scale, compared to the complete IDS and BAI which also cover somatic features of depressive and anxiety disorders. In addition, associations between multiple physical symptoms and recurrence of depressive and anxiety disorders remained statistically significant after adjusting for covariates such as residual depressive or anxiety symptoms. This indicates that multiple physical symptoms and depressive or anxiety symptoms are distinctive, but overlapping, concepts, and that multiple physical symptoms are related to recurrence of depressive and anxiety disorders regardless of residual depressive or anxiety symptoms. Simms et al. [34] studied whether somatic symptoms were statistically independent from depressive and anxiety symptoms and concluded that, although a general factor accounted for most of symptom variance, specific depressive and somatic symptomatology incrementally predicted psychosocial dysfunction and were specific to diagnoses of major depressive disorder and somatoform disorder, respectively.

Finally, when a cut-off score of 11 was used, the presence of multiple physical symptoms was not associated with recurrence of depressive and anxiety disorders over four years, after adjusting for covariates such as neuroticism. Explanations for this incongruence could be, for instance, that much information is lost when 4DSQ scores are dichotomized, or that neuroticism partly explained the

association between multiple psychical symptoms. The odds ratios in our continuous models were also attenuated in the adjusted models, which supports the latter explanation. Post-hoc regression analyses showed that neuroticism is related to multiple psychical symptoms at T0 ($r = 0.39$, $p < .001$; $\beta = 0.29$ [0.24 to 0.35], $p < .001$) and to depressive or anxiety disorders during four year follow-up (OR = 1.12 [1.09 to 1.15], $p < .001$), which is consistent with other studies [35-38]. These results suggest that the association between multiple psychical symptoms and depressive and anxiety disorders is confounded by neuroticism.

Strengths and limitations

One main strength of our study is that we used a prospective cohort, in which multiple physical symptoms, depressive and anxiety disorders were measured repeatedly over four years. Besides, recurrence of depressive and anxiety disorders was assessed by structured diagnostic interviews, covering the complete follow-up period.

However, our findings should be interpreted in the light of some limitations. First, participants who developed a depressive or anxiety episode between T0 and T2 may still have been depressed or anxious between T2 and T4. Theoretically, this cannot be seen as remission followed by recurrence but as one (chronic) depressive or anxiety episode. Sensitivity analyses, in which we excluded the data of the second period (T2-T4) of these participants, showed similar results (Appendix: Table 4). Second, multiple physical symptoms were measured with the 4DSQ somatization scale over the past week, which is rather short in relation to a two-year period between assessments. Also, the 4DSQ somatization scale does not establish whether physical symptoms are medically unexplained or whether participants sought help for these symptoms. Strictly speaking, it does not measure somatization but severity of physical symptoms.

Third, missing values were related to 4DSQ scores and diagnoses of depressive or anxiety disorders. For example, participants with a missing 4DSQ score were diagnosed with depressive or anxiety disorders more often. This may have resulted in an underestimation of the association between multiple physical symptoms and recurrence of depressive and anxiety disorders. However, the number of missing values was low, so in our opinion the effect of these selective missing values is small.

Further research and clinical implications

Although we studied longitudinal associations between multiple physical symptoms and recurrence of depressive and anxiety disorders during a four-year period, the number of measurements during this time period was limited. More longitudinal research on recurrence of depressive and anxiety disorders and its association with multiple physical symptoms is needed, with a higher number of repeated measurements. With well-founded knowledge about which risk factors play a role in

recurrence of depressive and anxiety disorders, prediction models for recurrence of depressive and anxiety disorders can be developed and validated. Such prediction models could establish patients' risk profiles, which allows for better targeted care for recurrent depressive and anxiety disorders according to these risk profiles.

In clinical practice, obtaining patients' 4DSQ somatization scores could indicate whether a patient is at risk of recurrence of depressive or anxiety disorders, and may facilitate the targeting of appropriate care [39]. In research, the 4DSQ could be a useful tool to explore the correlations and distinctions between somatization, distress, depressive and anxiety disorders.

Conclusions

From this prospective study we conclude that multiple physical symptoms were positively associated with recurrence of depressive and anxiety disorders over four years, regardless of residual depressive and anxiety symptoms. Knowledge of risk factors for recurrence of depressive and anxiety disorders, such as the presence of multiple physical symptoms, could provide possibilities for better targeting interventions to prevent recurrence. More research is needed to conclude on mechanisms by which multiple physical symptoms are related to (recurrence of) depressive and anxiety disorders.

ACKNOWLEDGEMENTS

The infrastructure of the NESDA study (www.nesda.nl) has been funded through the Geestkracht program of the Netherlands Organisation for Health Research and Development (Zon-Mw, grant number 10-000-1002) and participating universities (VU University Medical Center, Leiden University Medical Center, University Medical Center Groningen).

COMPETING INTERESTS

BT is the copyright owner of the 4DSQ and receives copyright fees from companies that use the 4DSQ on a commercial basis (the 4DSQ is freely available for non-commercial use in health care and research). BT received fees from various institutions for workshops on the application of the 4DSQ in primary care settings. The other authors have no competing interests to report.

REFERENCES

[1] Ormel J, Petukhova M, Chatterji S, Aguilar-Gaxiola S, Alonso J, Angermeyer MC, et al. Disability and treatment of specific mental and physical disorders across the world. *Br J Psychiatry* 2008;192(5):368-75.

- [2] Vos T, Barber RM, Bell B, Bertozzi-Villa A, Biryukov S, Bolliger I, et al. Global, regional, and national incidence, prevalence, and years lived with disability for 301 acute and chronic diseases and injuries in 188 countries, 1990–2013: a systematic analysis for the Global Burden of Disease Study 2013. *Lancet* 2015;386(9995):743-800.
- [3] Vos T, Haby MM, Barendregt JJ, Kruijschaar M, Corry J, Andrews G. The burden of major depression avoidable by longer-term treatment strategies. *Arch Gen Psychiatry* 2004;61(11):1097-103.
- [4] Mueller TI, Leon AC, Keller MB, Solomon DA, Endicott J, Coryell W, et al. Recurrence after recovery from major depressive disorder during 15 years of observational follow-up. *Am J Psychiatry* 1999;156(7):1000-6.
- [5] Keller MB, Boland RJ. Implications of failing to achieve successful long-term maintenance treatment of recurrent unipolar major depression. *Biol Psychiatry* 1998;44(5):348-60.
- [6] Cuijpers P, Beekman AT, Reynolds CF. Preventing depression: a global priority. *JAMA* 2012;307(10):1033-4.
- [7] Burcusa SL, Iacono WG. Risk for recurrence in depression. *Clin Psychol Rev* 2007;27(8):959-85.
- [8] Hardeveld F, Spijker J, De Graaf R, Nolen WA, Beekman AT. Prevalence and predictors of recurrence of major depressive disorder in the adult population. *Acta Psychiatr Scand* 2010;122(3):184-91.
- [9] Dijkstra-Kersten SM, Sitnikova K, van Marwijk HW, Gerrits MM, van der Wouden JC, Penninx BW, et al. Somatisation as a risk factor for incident depression and anxiety. *J Psychosom Res* 2015;79(6):614-9.
- [10] Kroenke K. Patients presenting with somatic complaints: epidemiology, psychiatric co-morbidity and management. *Int J Methods Psychiatr Res* 2003;12(1):34-43.
- [11] Tylee A, Gandhi P. The importance of somatic symptoms in depression in primary care. *Prim Care Companion J Clin Psychiatry* 2005;7(4):167-76.
- [12] Huijbregts KM, van der Feltz-Cornelis CM, van Marwijk HW, de Jong FJ, van der Windt DA, Beekman AT. Negative association of concomitant physical symptoms with the course of major depressive disorder: a systematic review. *J Psychosom Res* 2010;68(6):511-9.
- [13] Bekhuis E, Boschloo L, Rosmalen JGM, de Boer MK, Schoevers RA. The impact of somatic symptoms on the course of major depressive disorder. *J Affect Disord* 2016;205:112-8.

- [14] Stegenga BT, Kamphuis MH, King M, Nazareth I, Geerlings MI. The natural course and outcome of major depressive disorder in primary care: the PREDICT-NL study. *Soc Psychiatry Psychiatr Epidemiol* 2012;47(1):87-95.
- [15] Lok A, Assies J, Koeter MW, Bockting CL, Wouters LF, Mocking RJ, et al. Sustained medically unexplained physical symptoms in euthymic patients with recurrent depression: predictive value for recurrence and associations with omega 3- and 6 fatty acids and 5-HTTLPR? *J Affect Disord* 2012;136(3):604-11.
- [16] Penninx BW, Beekman AT, Smit JH, Zitman FG, Nolen WA, Spinhoven P, et al. The Netherlands Study of Depression and Anxiety (NESDA): rationale, objectives and methods. *Int J Methods Psychiatr Res* 2008;17(3):121-40.
- [17] Wittchen HU. Reliability and validity studies of the WHO - Composite International Diagnostic Interview (CIDI): a critical review. *J Psychiatr Res* 1994;28(1):57-84.
- [18] Terluin B, van Marwijk HW, Ader HJ, de Vet HC, Penninx BW, Hermens ML, et al. The Four-Dimensional Symptom Questionnaire (4DSQ): a validation study of a multidimensional self-report questionnaire to assess distress, depression, anxiety and somatization. *BMC Psychiatry* 2006;6:34.
- [19] Terluin B. De Vierdimensionale Klachtenlijst (4DKL): Een vragenlijst voor het meten van distress, depressie, angst en somatisatie [The Four-Dimensional Symptom Questionnaire (4DSQ). A questionnaire to measure distress, depression, anxiety, and somatization]. *Huisarts Wet* 1996;39(12):538-47.
- [20] Lipowski ZJ. Somatization: the concept and its clinical application. *Am J Psychiatry* 1988;145(11):1358-68.
- [21] Terluin B, Rhenen WV, Schaufeli WB, De Haan M. The four-dimensional symptom questionnaire (4DSQ): measuring distress and other mental health problems in a working population. *Work Stress* 2004;18(3):187-207.
- [22] Bonvanie IJ, van Gils A, Janssens KA, Rosmalen JG. Sexual abuse predicts functional somatic symptoms: an adolescent population study. *Child Abuse Negl* 2015;46:1-7.
- [23] Hardeveld F, Spijker J, De Graaf R, Hendriks SM, Licht CM, Nolen WA, et al. Recurrence of major depressive disorder across different treatment settings: results from the NESDA study. *J Affect Disord* 2013;147(1-3):225-31.
- [24] Scholten WD, Batelaan NM, van Balkom AJ, Wjh Penninx B, Smit JH, van Oppen P. Recurrence of anxiety disorders and its predictors. *J Affect Disord* 2013;147(1-3):180-5.

- [25] Costa PT, McCrae RR. Normal personality assessment in clinical practice: The NEO Personality Inventory. *Psychol Assess* 1992;4(1):5-13.
- [26] Pearlin LI, Schooler C. The structure of coping. *J Health Soc Behav* 1978;2-21.
- [27] Wiersma JE, Hovens JG, van Oppen P, Giltay EJ, van Schaik DJ, Penninx BW. The importance of childhood trauma and childhood life events for chronicity of depression in adults [CME]. *J Clin Psychiatry* 2009;70(7):983-9.
- [28] de Graaf R, Bijl RV, Smit F, Vollebergh WA, Spijker J. Risk factors for 12-month comorbidity of mood, anxiety, and substance use disorders: findings from the Netherlands Mental Health Survey and Incidence Study. *Am J Psychiatry* 2002;159(4):620-9.
- [29] Rush AJ, Giles DE, Schlessner MA, Fulton CL, Weissenburger J, Burns C. The inventory for depressive symptomatology (IDS): preliminary findings. *J Psychiatr Res* 1986;18(1):65-87.
- [30] Rush AJ, Gullion CM, Basco MR, Jarrett RB, Trivedi MH. The Inventory of Depressive Symptomatology (IDS): psychometric properties. *Psychol Med* 1996;26(3):477-86.
- [31] Beck AT, Epstein N, Brown G, Steer RA. An inventory for measuring clinical anxiety: psychometric properties. *J Consult Clin Psychol* 1988;56(6):893.
- [32] Kabacoff RI, Segal DL, Hersen M, Van Hasselt VB. Psychometric properties and diagnostic utility of the Beck Anxiety Inventory and the State-Trait Anxiety Inventory with older adult psychiatric outpatients. *J Anxiety Disord* 1997;11(1):33-47.
- [33] Wardenaar KJ, van Veen T, Giltay EJ, den Hollander-Gijsman M, Penninx BW, Zitman FG. The structure and dimensionality of the Inventory of Depressive Symptomatology Self Report (IDS-SR) in patients with depressive disorders and healthy controls. *J Affect Disord* 2010;125(1):146-54.
- [34] Simms LJ, Prisciandaro JJ, Krueger RF, Goldberg DP. The structure of depression, anxiety and somatic symptoms in primary care. *Psychol Med* 2012;42(1):15-28. doi: 10.1017/S0033291711000985.
- [35] Kotov R, Gamez W, Schmidt F, Watson D. Linking 'big' personality traits to anxiety, depressive, and substance use disorders: a meta-analysis. *Psychol Bull* 2010;136:768-821.
- [36] Klein DN, Kotov R, Bufferd SJ. Personality and depression: explanatory models and review of the evidence. *Annu Rev Clin Psychol* 2011;7:269-295.
- [37] Hyphanti T, Goulia P, Carvalho AF. "Personality traits, defense mechanisms and hostility features associated with somatic symptom severity in both health and disease." *J Psychosom Res* 2013;75(4):362-369.

[38] Russo J, Katon W, Lin E, Von Korff M, Bush T, Simon G, Walker E. Neuroticism and Extraversion as Predictors of Health Outcomes in Depressed Primary Care Patients. *Psychosomatics* 1997;38(4):339-348. [http://doi.org/10.1016/S0033-3182\(97\)71441-5](http://doi.org/10.1016/S0033-3182(97)71441-5).

[39] Geraghty AW, Stuart B, Terluin B, Kendrick T, Little P, Moore M. Distinguishing between emotional distress and psychiatric disorder in primary care attenders: A cross sectional study of the four-dimensional symptom questionnaire (4DSQ). *J Affect Disord* 2015;184:198-204.

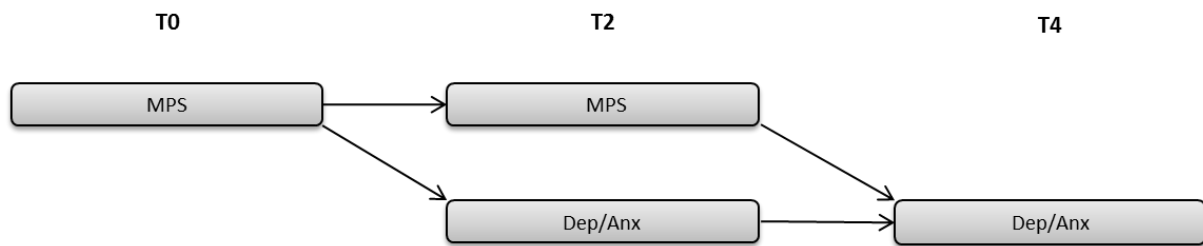


Figure 1: Time-lag model

T0: baseline assessment, T2: two-year follow-up assessment, T4 = four-year follow-up assessment,
MPS: multiple physical symptoms, Dep/Anx: recurrence of depressive or anxiety disorder

Table 1: Characteristics of the study sample at T0 (n = 584)

Characteristics	Mean (SD) or frequency (%)
Age, in years	44.2 (12.9)
Gender: female	415 (71.1%)
Education, in years	12.6 (3.19)
Number of chronic somatic diseases	
0	344 (58.9%)
1	166 (28.4%)
2 or more	74 (12.7%)
Neuroticism (NEO-FFI; 0-48)	20.7 (7.51)
Mastery (Pearlin mastery scale; 5-25)	18.9 (3.69)
Frequency of childhood trauma (n = 582)	
0	302 (51.9%)
1-2	135 (23.2%)
3-4	84 (14.4%)
5-6	50 (8.6%)
7-8	11 (1.9%)
Distress (4DSQ Distress; 0-28)	8.43 (6.59)
Multiple physical symptoms (4DSQ Somatization; 0-32)	7.82 (5.68)
Multiple physical symptoms (4DSQ Somatization, dichotomized; n=580)	
< 11	412 (71%)
≥ 11	168 (29%)
Frequent antidepressants use: yes	77 (13.2%)
Recency of last depressive or anxiety disorder episode	
more than 1 year ago	506 (86.6%)
less than 1 year ago	78 (13.4%)
Number of previous depressive episodes (n = 523)	
No previous episodes	115 (22.0%)
1 previous episode	235 (44.9%)
2 or more previous episodes	173 (33.1%)
Subclinical depressive symptoms (IDS-SR; 0-84)	14.0 (8.72)
Subclinical depressive symptoms (IDS-SR mood-cognition; 0-33)	3.99 (3.11)
Subclinical anxiety symptoms (BAI; 0-63)	7.07 (6.38)
Subclinical anxiety symptoms (BAI subjective scale; 0-21)	2.58 (2.68)

Table 2: Longitudinal associations of multiple physical symptoms (MPS) with recurrence of depressive and anxiety disorders (n=584)

	Depression		Anxiety		Depression or anxiety	
	OR (95% CI)	<i>p</i>	OR (95% CI)	<i>p</i>	OR (95% CI)	<i>p</i>
MPS						
<i>Unadjusted</i>	1.09 (1.06 to 1.12)	<.001	1.10 (1.07 to 1.14)	<.001	1.10 (1.07 to 1.13)	<.001
MPS						
<i>Adjusted for socio-demographics</i>	1.09 (1.06 to 1.12)	<.001	1.09 (1.06 to 1.13)	<.001	1.09 (1.07 to 1.12)	<.001
MPS						
<i>Adjusted for all covariates ^a</i>	1.04 (1.00 to 1.08)	.046	1.07 (1.03 to 1.12)	.001	1.06 (1.02 to 1.10)	.002
MPS						
<i>BAI / IDS replaced for BAI subjective scale / IDS mood-cognition ^a</i>	1.05 (1.01 to 1.09)	.018	1.07 (1.03 to 1.11)	.001	1.06 (1.02 to 1.09)	.001

^a adjusted for age, gender, education level, number of chronic somatic disorders, recency of the last depressive or anxiety episode, number of previous depressive episodes, subclinical depressive or anxiety symptoms at T0, neuroticism, mastery, and childhood abuse.

APPENDIX

Table 3: Longitudinal associations of multiple physical symptoms (MPS; dichotomous) with recurrence of depressive and anxiety disorders (n=584)

	Depression		Anxiety		Depression or anxiety	
	OR (95% CI)	<i>p</i>	OR (95% CI)	<i>p</i>	OR (95% CI)	<i>p</i>
MPS (>11)						
<i>Unadjusted</i>	2.41 (1.71 to 3.41)	<.001	2.40 (1.66 to 3.47)	<.001	2.39 (1.74 to 3.29)	<.001
MPS (>11)						
<i>Adjusted for socio-demographics</i>	2.39 (1.69 to 3.40)	<.001	2.24 (1.54 to 3.25)	<.001	2.30 (1.67 to 3.17)	<.001
MPS (>11)						
<i>Adjusted for all covariates ^a</i>	1.36 (0.88 to 2.10)	.169	1.42 (0.90 to 2.24)	.130	1.48 (0.98 to 2.25)	.064
MPS (>11)						
<i>BAI / IDS replaced for BAI subjective scale / IDS mood-cognition ^a</i>	1.48 (0.96 to 2.29)	.077	1.45 (0.93 to 2.29)	.105	1.54 (1.04 to 2.28)	.032

^a adjusted for age, gender, education level, number of chronic somatic disorders, recency of the last depressive or anxiety episode, number of previous depressive episodes, subclinical depressive or anxiety symptoms at T0, neuroticism, mastery and childhood abuse.

APPENDIX

Table 4: Sensitivity analysis (GEE in which the data of the second period (T2-T4) was excluded for participants ($n = 45$) who reported a depressive or anxiety episode at T2 and during T2-T4

	Recurrence of depression or anxiety	
	OR (95% CI)	p
Multiple physical symptoms <i>Unadjusted</i>	1.10 (1.07 to 1.13)	<.001
Multiple physical symptoms <i>Adjusted for socio-demographics</i>	1.10 (1.07 to 1.13)	<.001
Multiple physical symptoms <i>Adjusted for all covariates^a</i>	1.06 (1.02 to 1.10)	.005
Multiple physical symptoms <i>BAI / IDS replaced for BAI subjective scale / IDS mood-cognition^a</i>	1.06 (1.02 to 1.09)	.002

^a adjusted for age, gender, education level, number of chronic somatic disorders, recency of the last depressive or anxiety episode, number of previous depressive episodes, subclinical depressive and anxiety symptoms at T0, neuroticism, mastery and childhood abuse.